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Technical note

Vertebral stiffness measured via tomosynthesis-based digital volume correlation is strongly correlated with reference values from micro-CT-based DVC

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ABSTRACT

Digital tomosynthesis (DTS) is a clinically available modality that allows imaging of a patient's spine in supine and standing positions. The purpose of this study was to establish the extent to which vertebral displacement and stiffness derived from DTS-based digital volume correlation (DTS-DVC) are correlated with those from a reference method, i.e., microcomputed tomography-based DVC (μ CT-DVC). T11 vertebral bodies from 11 cadaveric donors were DTS imaged twice in a nonloaded state and once under a fixed load level approximating upper body weight. The same vertebrae were μ CT imaged in nonloaded and loaded states ($40\ \mu\text{m}$ voxel size). Vertebral displacements were calculated at each voxel using DVC with pairs of nonloaded and loaded images, from which endplate-to-endplate axial displacement (D_{DVC}) and vertebral stiffness (S_{DVC}) were calculated. Both D_{DVC} and S_{DVC} demonstrated strong positive correlations between DTS-DVC and μ CT-DVC, with correlations being stronger when vertebral displacement was calculated using the median ($R^2=0.80$; $p<0.0002$ and $R^2=0.93$; $p<0.0001$, respectively) rather than average displacement ($R^2=0.63$; $p<0.004$ and $R^2=0.69$; $p<0.002$, respectively). In conclusion, the demonstrated relationship of DTS-DVC with the μ CT standard supports further development of a biomechanics-based clinical assessment of vertebral bone quality using the DTS-DVC technique.

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1. Introduction

Vertebral fractures are the most common type of osteoporotic fracture [1–4], and cause persistent back pain and spinal deformity which can further lead to other complications such as pulmonary [5–7] and gastroesophageal [8] problems. A vertebral fracture is also a predictor of future fractures [9–11], the risk being particularly high for additional future vertebral fractures [9,12–15]. As such, prevention of vertebral fractures is important for preventing the associated complications and, potentially, more debilitating fractures.

One important aspect of prevention is identification of those who are at risk of fracture. Bone mineral density (BMD) as measured from dual x-ray absorptiometry (DXA), which is currently used as the standard assessment of osteoporosis, is not accurate in predicting vertebral fracture, with about 60% of fracture cases being non-osteoporotic according to their T-score [16]. In laboratory experiments, while BMD can explain about 35–70% of

the variability in vertebral strength [17–21], stiffness is generally found to be the strongest non-destructively measurable correlate of vertebral strength [22,23]. One way of estimating vertebral stiffness and strength using clinically available modalities is quantitative computed tomography (CT) based finite element (FE) modeling, which has been successful in predicting vertebral strength [23–25] and fracture risk [26,27]. However, FE models require assumptions about material property and loading that may result in a poor estimation of displacements within the vertebral body [28]. Additionally, levels of radiation exposure from CT imaging may limit routine use of CT-based finite modeling. As such, the need for a clinically feasible method for directly assessing the biomechanical integrity of a vertebra with low radiation exposure continues to exist.

Digital volume correlation (DVC) is a method appropriate for quantifying displacements in structures with texture. In this technique, images taken under mechanical load are correlated to those taken without mechanical load for the same object and the image texture differences are used to calculate displacement of individual points in the structure. A noteworthy feature of DVC is its sub-voxel precision for displacements [29], which makes it additionally

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attractive for applications where displacements are small relative to voxel size, as is typically the case in clinical image modalities. Originally described for microcomputed tomography (μ CT) applications [30], DVC remained a powerful tool for laboratory research [31–36] with virtually no clinical applicability to the spine due to lack of clinical imaging modalities suitable for spinal DVC measurements. We have recently described a DVC approach for measuring vertebral displacements based on digital tomosynthesis (DTS) in a proof of concept study [37]. In that study, we have shown in vitro and in vivo representative cases to support feasibility of using a clinical DTS imaging modality for DVC analysis of human vertebrae. We also demonstrated a strong correlation between intra-vertebral displacements measured from DTS and those measured from reference μ CT measurement in a single vertebra. However, this demonstration was not substantiated for endplate-to-endplate displacements and vertebral stiffness as single outcomes for a given vertebra using multiple specimens. The information on the strength of the relationship between DTS- and μ CT-derived variables is important for an informed utilization of DTS-DVC as a bone assessment tool in future clinical applications. Therefore, the objective of this study was to correlate measurements of vertebral displacement and stiffness derived from DTS based DVC (DTS-DVC) and those from μ CT based DVC (μ CT-DVC) to determine the strength of association between the two measurements.

2. Materials and methods

Under institutional review board approval, eleven human cadaveric T11 vertebrae were utilized (6 Females, 5 Males; 62–96 years old). Donors with a history of infectious diseases, metabolic diseases known to affect bone, corticosteroid use, or spinal surgery, or cause of death involving trauma were excluded. Vertebral bodies were dissected and removed of soft tissue. Due to size constraints imposed by the μ CT system, and to maximize the resolution in the μ CT-based reference measurements, posterior elements were removed prior to imaging studies.

DTS-DVC imaging of vertebral bodies was performed in a custom radiolucent loading chamber that was designed to accommodate imaging in both DTS and μ CT systems as previously described in detail [37]. Briefly, vertebral endplates were potted using a rigid filler material (Bondo Corp, Atlanta, GA) to ensure flat boundary conditions, and the entire load frame was placed in the imaging system (Shimadzu Sonialvision Safire II), while the scanner was kept in the vertical position. Specimens were imaged twice in non-loaded state. Specimens were then loaded using weight plates to a fixed load level approximating upper body weight (445 N generated by a stack of five 20 lb [9 kg] weight plates) and rescanned, with 10 min wait between loading and imaging to allow for displacement to stabilize. Clinical protocols for adult DTS examinations of the spine were followed during acquisition [37]. Acquisition time for each DTS scan was less than three seconds. A filter consisting of 0.5 mm copper plus 1 mm type 1100 aluminum was added to the x-ray tube collimator to simulate the attenuation of the x-ray beam by an adult abdomen [38].

Following the DTS-DVC imaging, the specimens were moved to the custom μ CT system described previously [39], and a nonloaded image was acquired at 40 μ m voxel size using the same chamber used in DTS imaging (80 kV, 63 μ A, reconstructed from 720 projection views acquired over 360° at 4 s per view). The vertebra was then reloaded to the same load level applied during DTS imaging which was held for 10 min, and the loading piston in the chamber was locked in place prior to the loaded image acquisition. Finally, a loaded image of the vertebra was acquired in the μ CT system. The vertebrae were kept moist using saline-soaked towels enclosed in the loading chamber during all DTS and μ CT imaging studies.

DTS images were reconstructed at 0.28/0.28/1 mm voxel spacing (corresponding to superior-inferior/lateral-medial/anterior-posterior directions) and resampled to isotropic voxel size (0.28 mm), registered using a 3D region at the inferior endplate (MIPAV, NIH, Bethesda, MD), and scaled to match for the mode and standard deviation of gray level distributions. Displacements were measured at every other voxel along a grid of reference points using the methods and DVC software described extensively in previous work [29,37]. Briefly, DVC performs full-grayscale correlations between spherical test regions (radius=4 mm) in nonloaded and loaded volumes, using the nonloaded volume as the reference grid. The grayscale values at fractional locations are estimated by fitting a tri-cubic spline to the 4 voxel³ cube of grayscale values surrounding the fractional location. The program adjusts the X-, Y- & Z-displacement coordinates for that point in the model using a steepest-descent algorithm to maximize the correlation value between the reference region in the nonloaded volume and the corresponding target region in the loaded volume. Vertebral displacement (D_{DVC}) was calculated as the average of the axial displacement distribution at the superior endplate as in previous work [37], and alternatively as the median of the distribution owing to the nonnormal nature of the distribution. Stiffness (S_{DVC}) was calculated by dividing the applied load (445 N) by D_{DVC} . DVC analysis of μ CT images was similar, except resampling to isotropic voxel size was not necessary. DVC analyses were performed on a HP G6 Z4 workstation configured with dual 2.2 Ghz Intel Xeon 4114 processors (40 threads total) and 64 GB RAM.

The pairs of nonloaded DTS images were similarly processed using DVC to assess numerical precision of the method. Accuracy and precision of the vertebral displacement measurements were calculated as average and standard deviation, respectively, of D_{DVC} across the 11 specimens (with the expectation being zero mean displacement) [29,30,32,40,41]. Total error was expressed as the square root of the sum of squared accuracy and precision [42]. Regression analysis was used to examine the relationship between DTS and μ CT derived variables.

3. Results

The spatial distribution of axial displacements agreed well qualitatively between μ CT and DTS, based on displacement gradients of similar nature in both images (Fig. 1). (For example, there is a gradient of increasing displacement from the lower endplate towards the center of the upper endplate, with similar transition patterns in both images, for the case presented in Fig. 1).

Vertebral displacements calculated using DTS-DVC demonstrated a strong positive correlation with μ CT displacements, the correlation being stronger when the median value of displacements measured at the top endplate axial plane was used compared to the average of the distribution ($R^2=0.80$; $p<0.0002$ and $R^2=0.63$; $p<0.004$, respectively) (Fig. 2).

The distribution of axial displacements measured from non-loaded comparisons (i.e., noise) was well separated from the distribution of displacements measured under load (Fig. 3). Accuracy and precision of the DTS-DVC based vertebral displacement was $-3.2 \mu\text{m}$ and $11.3 \mu\text{m}$ giving a total error of $11.7 \mu\text{m}$ when calculated from the median, and $-3.2 \mu\text{m}$ and $11.6 \mu\text{m}$ giving a total error of $12.0 \mu\text{m}$ when calculated from the average of the endplate displacement distributions.

The relationship between vertebral stiffness calculated from DTS-DVC and that from μ CT-DVC was even stronger ($R^2=0.93$; $p<0.0001$ and $R^2=0.69$; $p<0.002$, for median and average displacements, respectively) (Fig. 4). Although this study was not designed to test differences between sexes, it is important to note that the data are not clustered by sex about the regression line for both stiffness and displacements (Figs. 2–4).

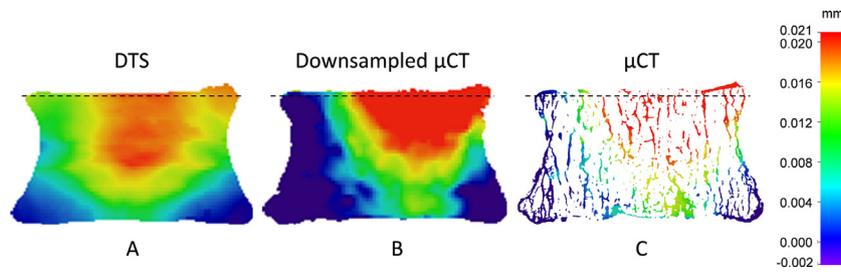


Fig. 1. Volumetric average and median of axial displacements (region indicated by dotted line) was calculated from DTS (left) and μ CT (right) DVC solutions. For ease of interpretation, the μ CT image has been downsampled to DTS resolution using reciprocal distance squared weighted interpolation (center). DTS axial displacement values have been scaled to the same range as μ CT for visual comparison of the spatial distributions of displacement. In the color bar, compressive axial displacements are positive.

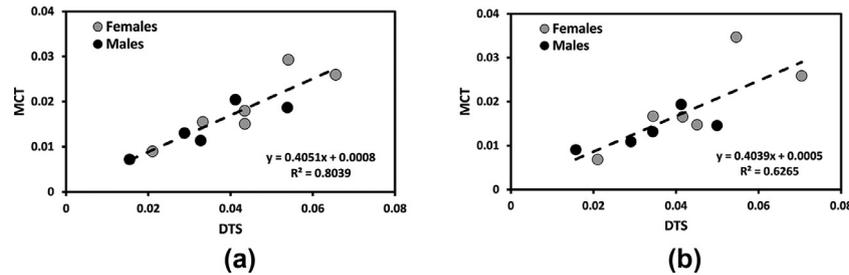


Fig. 2. The relationship between μ CT- and DTS-measured displacements (mm) using a) the median of the endplate displacement distribution and b) the average of the endplate displacement distribution.

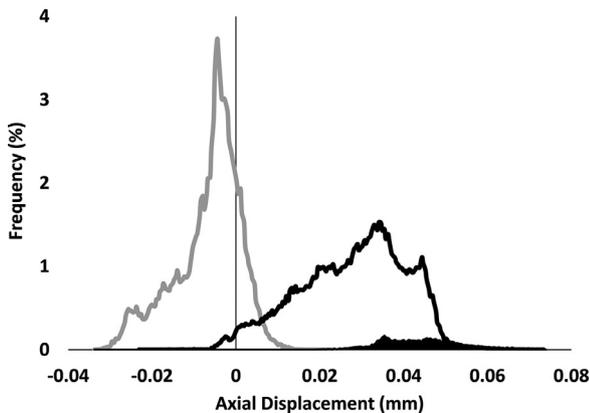


Fig. 3. Typical histogram of DTS-DVC derived axial displacements measured under no load (gray outline) and 445 N load (black outline) for the same bone. The distribution of endplate-to-endplate displacements (black filled) is well separated from the noise distribution. For all distributions, frequency is expressed as a percentage of the overall number of vertebral bone voxels.

For diagnostic purposes, to understand the main results better, we correlated the median with average vertebral displacements within each method and found that they agreed better for DTS ($R^2=0.996$, slope=0.988) than for μ CT ($R^2=0.738$, slope=1.012).

For DTS-DVC calculations, computational time was 46 ± 13 min with peak memory usage < 2 GB for all trials. For a skilled opera-

tor, approximately 10 min of user interaction is required per specimen for image pre-processing, preparation of parameter files as input to the DVC software, and post-processing DVC output.

4. Discussion

In the current study, we demonstrated that vertebral endplate-to-endplate displacement and stiffness quantified using DTS-DVC correlate well with reference measurements from μ CT-DVC. The strong correlation between DTS-DVC and μ CT-DVC supports the feasibility of measuring displacement of a vertebra under load and its stiffness using the clinically available DTS imaging methods and a direct mechanical approach.

Using the median of the endplate displacement distribution in the calculation of vertebral displacement and stiffness resulted in a stronger relationship between DTS and μ CT than using the average. This might be attributable to the ability of a median filter to remove outliers more effectively, and the median being a better measure of central tendency than the mean when the distribution of the values is nonnormal (Fig. 3). Outlying values are more expected for the μ CT solutions due to the high spatial resolution of μ CT images [43], as indicated by a less well-correlation than DTS solutions between the median and average endplate displacements. As such, the median appears preferable for obtaining a single value to represent the displacement of the entire vertebral body in DVC applications.

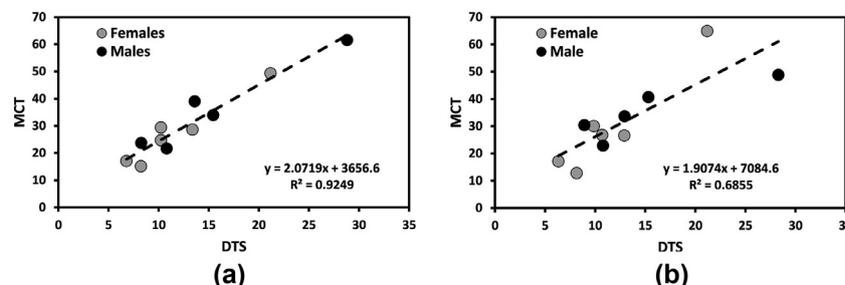


Fig. 4. The relationship between μ CT- and DTS-measured stiffness (kN/mm) using a) the median of the endplate displacement distribution and b) the average of the endplate displacement distribution.

The stiffness values measured via DTS were comparable to those reported in literature for human vertebrae including T11-L4 levels (6.44–40.4 kN/mm) [44], albeit on the higher side. Distinctions between stiffness measured from DVC and stiffness measured from uniaxial compression testing must be noted when comparing the results. First, as the vertebral displacement is calculated only within the bone phase, stiffness values calculated from DVC represent structural stiffness isolated from machine compliance and contribution from soft tissue, potting medium, and other factors external to bone. In finite element models with the assumption of rigid bonding between the filler and the bone, it is common to observe stiffness values about 3 times higher than those measured in a materials test machine [45]. In addition, vertebral displacement is calculated in a plane just below the endplate in DVC, thereby eliminating the contribution of epiphyseal ring displacements, potentially resulting in a further decrease in the measured apparent displacement compared to the experiments in a materials test machine [46].

Reference stiffness values calculated from μ CT were consistently higher than those from DTS, corresponding to lower displacement measurements for μ CT than for DTS. This disagreement is partially attributable to the effect of a substantial difference in resolution between the two modalities. In addition, the displacement locking mechanism used during μ CT scans resulted in a systematically lower displacement than intended in μ CT-DVC, further contributing to a numerical disagreement between measured magnitudes. Using the locking mechanism was necessary due to the inability of the μ CT stage to carry load plates, and substantially longer acquisition time for μ CT images compared to DTS images. Correcting for this displacement due to locking did not affect the R^2 values and improved the numerical agreement between the two modalities (see Supplemental Data). Despite a slight improvement in numerical agreement (μ CT stiffness was reduced by approximately 20%), the correction was not sufficient to bring μ CT and DTS values to the same level. The regression equations relating μ CT (corrected) and DTS values may be considered in the interest of calibrating the magnitude of the DTS-DVC solution. However, the data presented in this work is considered valid on the basis of correlative findings and the strong linear relationship found between the two modalities supports the use of DTS-DVC for a stiffness based assessment of vertebral quality.

Alternatively, measurements from a materials test machine could be used as reference for bulk measurements of vertebral displacement and stiffness. However, the use of μ CT based DVC was preferred as a compatible reference standard to DTS-DVC, for the reasons argued above as potentially affecting stiffness measurements in a materials test machine. These effects can be large under a small load (and of unpredictable magnitude for each specimen). In addition, by using a μ CT based DVC reference standard, the current work can be extended to examination of intravertebral strains. This information would be useful in the identification of intravertebral regions that are at higher risk of failure.

Total error in the current dataset is higher than that determined in a smaller sample [37]. Despite this, the displacement error of the DTS-DVC method was about 40 times smaller than the yield displacement of a vertebral body observed in uniaxial compression tests using boundary conditions similar to those used in the current study (yield displacement = 0.496 ± 0.095 mm from 27 human cadaveric L1 vertebrae tested in our laboratory in an unrelated experiment, unpublished data). It must be noted that this is the between-specimen measurement error for endplate-to-endplate vertebral displacement used in the calculation of stiffness. The accuracy and precision for local displacements will be further evaluated in subsequent work with the relevant focus.

A major limitation of this work is that it was conducted using a known load level of 445 N. This load magnitude is consid-

ered to be physiologically relevant for standing [47,48] and therefore the displacements measured under this load are also considered to be physiologically relevant. Using a known load allowed us to examine the capability of the DTS-DVC in isolation, as estimation of loads in a clinical application is generally made outside of the DTS system. Our vision for this method as a clinical test is performing DVC between horizontal (patient lying) and vertical (patient in neutral standing) DTS images. For this configuration, vertebral loads can be approximated by using body weight and anthropometric measurements [49–51], although it can be more complex during other tasks [49,52]. It should be emphasized that vertebral displacement alone, without calculating stiffness, may be an informative parameter, as it is a composite measure of intrinsic (stiffness) and extrinsic (loading) properties of the vertebra, similar to the concept of factor of safety. Nonetheless, it remains to be determined to what extent patient-specific loading complicates the DTS-DVC calculations and affects its utility as a bone assessment tool.

DVC calculations were performed using the set of parameters presented in previous work [37]. Parameters were optimized to minimize combined accuracy and precision error of intra-vertebral displacements. For parameters which had minimal effect on displacement error, such as reference grid spacing, we selected those that minimize solution time, as this is a relevant concern for an application envisioned to be a clinical tool. Although solving at a finer grid spacing would provide additional resolution for assessing the correspondence in terms of local, subregional deformations between micro-CT and DVC, this was not the subject of this paper but may be explored in future work. The stiffness measurement presented in the current study is derived using the axial displacement from a large number of reference points (the average/median top endplate alone comprises >12,000 data points). When averaging over a large number of reference points, there is minimal benefit to additional accuracy when weighed vs. solving time.

Although traditionally osteoporosis assessment from the spine involves lumbar vertebrae, T11 vertebral bodies were used due to their smaller size in this validation study, in order to maximize image resolution in the reference μ CT measurements. Though not a common site for assessment for osteoporosis, fractures of T11 are also common [53] and as such this site is considered to be relevant in the context of this study. Nonetheless, in future studies that don't require concomitant assessment with μ CT, consideration of the lumbar vertebrae would be possible, as was demonstrated in a pilot in vivo study [37].

In conclusion, the current data support that a direct biomechanical examination of vertebral bone is feasible using DTS-DVC based estimations of vertebral displacements. Future studies will examine the clinical validity of the present findings from in vitro work, and attempt to expand the analysis techniques to local displacements and strains.

Ethical approval

Not required.

Declaration of Competing Interest

The authors have received no conflicting financial benefit from this work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.medengphy.2020.08.008.

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